Chemotherapy in Malignant Mesothelioma: What's Up, Doc?

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Two randomized trials have now established the combination of cisplatin and an antifolate—pemetrexed or raltitrexed—as the standard in the systemic therapy for mesothelioma.[1,2] There remains however a large number of issues to be addressed. Not the least is whether the choice of the control arm in both trials was appropriate, in the absence of studies having compared active supportive care (ASC) with and without chemotherapy. An ongoing study by the British Medical Research Council (MRC)—randomizing between ASC, ASC with single agent vinorelbine and ASC with mitomycin, vindesine and cisplatin (MVP)—will hopefully address the issue in analogy to what has been observed in non-small cell lung cancer (NSCLC). In the mean time, indirect evidence comes from both abovementioned trials, as it is unlikely that single agent cisplatin will reduce survival in this patient population. Furthermore, a recent small randomized study comes closest to answering the question.[3] Good performance patients with stable symptoms were randomized between immediate chemotherapy, consisting of MVP, or the same chemotherapy at symptomatic progression. In the latter arm, chemotherapy was delayed with a median of 4 months, and five patients never received any. In those who actually received chemotherapy, immediate treatment was associated with a significantly longer time to symptomatic progression and a trend to improved overall survival: 66% at 1 year compared to the "delayed" patients (36%), whose quality of life was less well maintained. Whether the true improvement in median survival with chemotherapy will be in the observed magnitude of 3–4 months is doubtful. As is the case in advanced NSCLC, the estimated median improvement in a general mesothelioma population eligible for platinum-based chemotherapy will probably average 8–10 weeks.

The next issue then becomes what to consider as the standard regimen. Although strictly speaking, head-to-head comparisons between cisplatin/pemetrexed, cisplatin/raltitrexed, MVP, or vinorelbine need to be conducted, it is foreseeable that, also in analogy with NSCLC, none of these regimens will prove to be superior and that criteria other than outcome will become decisive: toxicity, compliance, ease of administration. Determining whether this amounts to a noninferiority of these regimens will require trials with sample sizes that are out of reach for a disease that is rare.

Similarly, in view of their observed single agent activity in mesothelioma, one might question whether single-agent pemetrexed or raltitrexed would not have been the better comparator in the randomization.[4,5] The use of single agent cisplatin, although moderately active, is distinctly unusual in current practice. Most clinicians would have associated either a third generation drug or an anthracycline.

What is the impact of the administration of vitamins on mesothelioma chemotherapy? Although there is no scientific rationale that vitamins per se are active against mesothelioma, one could argue that systemic toxicity might be affected by vitamins. B12 and folic acid could "rescue" the bone marrow. In the pemetrexed study, patients on the cisplatin only arm appeared to have improved their toxicity profile when given vitamins.[1]

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Furthermore, the statistical significance in outcome was lost in the subgroup of patients supplemented with vitamins. This might reflect a loss of power by the smaller sample size, a neutralization of the activity of pemetrexed, or a potentiation of the activity of cisplatin. The latter explanation is doubtful because responses and outcome in the cisplatin arms are similar in both folate trials.

What is the optimal dose of the antifolates? The phase I studies defined a maximum tolerated dose (MTD) based on pemetrexed being given without vitamin support. With vitamin support, it appears that the MTD would be much higher. The results of a randomized trial exploring two dose levels of pemetrexed with cisplatin and vitamins are expected. It is tempting to speculate that a subgroup of patients with high concentrations of intracellular target enzymes could benefit more from higher doses of antifolates when adequately substituted with vitamins. Pharmacogenomically tailored antifolate administration might then well open new treatment perspectives.

A next set of issues is reminiscent of hypotheses already investigated at length in NSCLC: duration of treatment, value of maintenance single agent antifolate, cis- or carboplatin based regimens, drug substitution, platinum versus nonplatinum based regimens, adding a third agent to an active doublet. The pemetrexed study reached a median number of cycles of six, compared with four with cisplatin/raltitrexed. Trials looking at the optimal number of cycles should start from these figures and compare them with either more or fewer cycles. A preliminary uncontrolled report of maintenance pemetrexed in 13 patients obtaining response after induction combination treatment shows a better outcome as compared to 14 patients not treated with maintenance.[6] There are promising phase II results with combinations of pemetrexed combined with oxaliplatin, carboplatin or gemcitabine. [7–9] The latter two combinations will move into a comparative trial. It is however, regrettably foreseeable that the outcome of these issues will not be different from those observed in NSCLC: all platinum based combinations are equivalent, platinum and nonplatinum are equivalent, all doublets are equivalent and triplets add nothing but toxicity. One might even question whether trials investigating such comparisons need even to be performed in the light of the small number of patients available for clinical trials.

Novel antifolates are being designed using a high resolution crystal structure of the intracellular enzymes involved in folate metabolism. Improvements in chemotherapy for mesothelioma might primarily come from the use of molecularly targeted drugs such as nolatrexed, binding to the folate cofactor binding site of thymidilate synthase.[10] Unfortunately its development was halted after negative studies.[11]

With the high response rate observed with cisplatin-antifolate combinations, investigators recently turned to these regimens as neoadjuvant ones. Two multicentric series in early stage patients have been reported so far, observing a response rate of 32–40%.[12,13] The regimens appeared safe, with a high number of patients having resections. Contrary to observations in other neoadjuvant series, no pathologic complete remission or evidence of tumor necrosis, was reported in the resection specimens. The report in this issue by Flores et al. illustrates the challenges faced by investigators with this multimodality approach in more advanced stages.[14] Only seven of the 37 patients who initially were supposed to be accrued underwent the full therapy that the trial was designed to evaluate. The true value of induction chemotherapy in a multimodality setting will, however, have to wait for the results of phase III trials, one of which has recently started[15]

Despite doubts about the design of both published randomized trials, cisplatin and an antifolate should be considered the standard-of-care, first-line treatment of selected patients with malignant mesothelioma against which future treatments will have to be compared. The odds are against major further improvements by substitution of drugs or new combinations of existing drugs. Further progress should come from the (addition of) novel drugs or targeted agents, first to be tested in refractory patients.

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